TRANSDERMAL THERAPEUTIC SYSTEM COMPRISING A RESERVOIR-TYPE PRESSURE-SENSITIVE ADHESIVE LAYER AND A BACK LAYER WITH UNI-DIRECTIONAL RESILIENCE

The invention relates to a transdermal therapeutic system, in particular an active substance patch, comprising a redetachable protective layer, a pressure-sensitive reservoir layer and a backing layer with or without a coating of pressure-sensitive adhesive. The invention also relates to a process for producing such a transdermal therapeutic system [occasionally abbreviated to TTS below] and to the use thereof.

A TTS is a skin-applied administration form for active substances for delivery through the skin, and has the appearance of traditional patches. It ought to be distinguished from a topical active substance plaster - for example, a rheumatism plaster or a corn plaster. A TTS of this kind can include one or more active substances which are delivered continuously over a fixed period at a predetermined rate to the site of application ("Heilmann, Klaus: Therapeutische Systeme - Konzept und Realisation programmierter Arzneiverabreichung" [Therapeutic systems - design and implementation of programmed drug administration], 4th edition, 1984, Ferdinand-Enke-Verlag, Stuttgart). The fixed period referred to above is usually 24 hours. For the treatment of chronic disorders, however, it is necessary to administer medicaments for a longer period. It may therefore be appropriate to apply a TTS for a period longer than 24 hours, since this is more likely to result in constant plasma levels.

A typical such transdermal therapeutic system in the form of a patch is known from EP-B 0 430 019. It has a backing layer which is impermeable to the active substance, a

pressure-sensitive adhesive reservoir layer, and a redetachable protective layer. The active-substance-impermeable backing layer can be composed of flexible or inflexible material. Substances which it is mentioned are used for producing such materials are polymer films or metal foils or else a composite comprising a film which has been coated with aluminium by vapour deposition. Where such systems are worn on the skin for a prolonged period, as is necessary (as mentioned above) for treating chronic disorders in particular, a pronounced sensation of a foreign body is perceived on the skin within a short time, owing to the relative rigidity of the TTS. This is extremely unpleasant for the user.

Another embodiment of such a TTS is described in US-A 5,246,705. The transdermal system it describes has an elastomeric backing layer having a defined vapour transmission rate in the range from 0.1 to 20 $g/m^2/hr$ and a Young's modulus in the range of about 10^4 to 10^9 $dynes/cm^2$. Particularly preferred materials for the elastomeric backing layer are, for example, A-B-A block copolymers, the A blocks comprising styrene and the B blocks saturated hydrocarbon polymers such as, for instance, ethylene-butylene copolymers, ethylene-propylene copolymers, and the like. When the transdermal therapeutic systems as per the said US-A 5,246,705 are worn on the skin for a prolonged period, again, it is impossible to avoid the above-described sensation of a foreign body.

US-A 4,780,168 discloses a strip-like wound bandage for sealing wounds, which is fabricated from a woven or non-woven, polymer-based material, the said material having a planar stretching characteristic in the range from 0.5 to 110 [pounds/inch]. Materials of such extensibility are, however, not immediately suitable as materials for backing

layers of transdermal therapeutic systems. Either their extensibility is too low, in which case the unpleasant foreign-body sensation described above is felt when they are worn on the skin for a prolonged period, or else they are much too extensible, in which case the production of transdermal therapeutic systems is accompanied by the so-called curling effect, which is explained below.

During the production of the laminate from which the individual active substance patches are punched, the material for the backing layer comes under tensile stress and the resulting elastic return force means that, during punching, the opposite ends of the patches are each bent up. Owing to the reject rate during manufacture, this effect results in high costs, together with unnecessary environmental burden.

Aside from the abovementioned disadvantages, a material for the backing layer of a wound bandage is also unsuited to a TTS for other reasons too, such as the required impermeability to active substance.

The object of the invention is therefore to provide a transdermal therapeutic system which comprises a redetachable protective layer, a pressure-sensitive adhesive reservoir layer and a backing layer with or without a coating of pressure-sensitive adhesive and which avoids the aforementioned disadvantages. In particular, there should be no sensation of a foreign body on the skin in the course of prolonged wearing, even for periods of from several days to about 1 or 2 weeks. Furthermore, the production of the TTS should not be accompanied by the curling effect, so ensuring rational and inexpensive production.

This object is achieved in accordance with the invention by a transdermal therapeutic system, in particular an active substance patch, which comprises a redetachable protective layer, a pressure-sensitive adhesive reservoir layer and a backing layer with or without a coating of pressure-sensitive adhesive, the backing layer being of a unidirectionally, especially longitudinally, elastic material having an elasticity of at least 20%.

Preferred embodiments of the TTS of the invention are subject-matter of the dependent claims.

In accordance with the invention, the TTS features not only a redetachable protective layer and a pressure-sensitive adhesive reservoir layer but also a backing layer which, optionally, is likewise coated with pressure-sensitive adhesive and which has a specifically defined unidirectional elasticity. With regard to the TTS of the invention, the elasticity is determined in accordance with the DIN standards 60 000 and 61 632 (April 1985), which are conventionally used for elasticity tests. Originally, these DIN standards do in fact apply to ideal bandages; the horizontal force extension unit used to test the elasticity can, however, be employed analogously for other materials as well. In accordance with the invention, the backing layer of the TTS is elastic in only one direction, i.e. in longitudinal or transverse direction. Relative to the longitudinal axis of the TTS, the transverse axis is that lying at right angles to it. In a circular TTS, the longitudinal and transverse axis are of course identical in length. In particular, the backing layer material used in accordance with the invention is unidirectionally longitudinally elastic.

In the other direction, the backing layer is nonelastic. Nonelastic means that no elasticity can be found when testing by hand. In the case of measurement in accordance with DIN 61 632, then, the elasticity is less than 20%. In accordance with the invention, therefore, the elasticity in one direction - mainly the elastic direction - is above 20%.

Since the production of the patch involves it being punched out from a laminate, it would also be possible to conceive in principle of the TTS being "unidirectionally" elastic at an angle to the longitudinal direction of the patch. Oblique elasticity of this kind is, however, the result of a superposition of elasticity in the transverse <u>and</u> longitudinal directions.

In the TTS of the invention, the elasticity of the unidirectionally elastic material used for the backing layer is preferably less than 150%. In a more preferred embodiment the elasticity is in the range from 20 to 80%, with particular preference in the range from 40 to 70%. The most preferred elasticity for a backing layer material, and, accordingly, that which is most advantageous for the achievement of the object on which the invention is based, lies within the range between 44 and 56%, always measured in accordance with DIN 61 632.

Preferred materials for the unidirectionally elastic backing layer are those which are microbially nondegradable. The material should be more than 90%, preferably more than 99%, microbially nondegradable. The degradability can be measured by conventional methods familiar to the person skilled in the art. Low degradability is particularly important in the case of TTSs which are to be worn on the skin for a prolonged period.

The reason for this is that, owing to the transpiration of the skin, a microclimate in which bacteria, fungi, spores etc. absolutely thrive develops directly below the section of skin covered by the TTS. Consequently, low microbial degradability, especially in the case of prolonged wearing, is extremely advantageous. The material of the backing layer can be a woven fabric, a nonwoven fabric or a film. Where the backing layer comprises a polymer, the said polymer is selected advantageously from polyethylene, polypropylene or polyesters, especially polyalkylene terephthalates.

A number of polymeric materials may be mentioned by way of example for the backing layer. Advantageous polymeric materials which meet the above requirement of low microbial degradability are polyterephthalic diesters obtainable by the reaction of a starting material selected from ethylene glycol, 1,4-butanediol, 1,4-dihydroxymethylcyclohexane, terephthalic acid, isophthalic acid, adipic acid, azelaic acid, sebacic acid, dimethyl terephthalate, dimethyl azelate, dimethyl sebacate, bisphenol A diglycidyl ether, n-decane-1,10-dicarboxylic acid, polyethylene glycol and polybutylene glycol.

In the transdermal therapeutic system of the invention, it is likewise possible for a further separating layer to be arranged between backing layer and reservoir layer for the purpose, for example, of preventing active substance permeability. In this case, the backing layer on the skin-facing side, and/or the separating layer on the distal side, are/is likewise coated with pressure-sensitive adhesive.

For the effectiveness of a TTS of the invention it is advantageous for the backing layer to project beyond the

reservoir on all sides. This has the advantage that there are no losses of active substance in the lateral direction. Furthermore, the TTS of the invention can be produced in a particularly inexpensive manner in this case, since the sections containing active substance can be punched separately. This avoids expensive, environmentally harmful, leftover waste pieces containing active substance. The backing layer of the TTS has a water vapour permeability of at least 0.1 $g/m^2/h$, preferably from 1 to 20 $g/m^2/h$.

Where a woven or nonwoven fabric or else a porous film is used, the porosity lies within the range from 10% to 50%. Porosity here means the proportion of pores having an area of $\leq$ 400 μm^2 as a percentage of the reference area in question. This relative pore area can be determined by measuring and counting the pores of any unextended reference area under the microscope or a thread counter.

If a woven fabric is used for the transdermal therapeutic system (TTS) of the invention, the backing layer has a number of warp threads in the range of 300-350, preferably in the range of 310-330, and/or a number of weft threads in the range from 100 to 140, preferably in the range from 120 to 130, measured in each case per 10 cm of unextended fabric.

The pressure-sensitive adhesive reservoir layer of the transdermal therapeutic system of the invention comprises at least one active substance. This substance is preferably selected from the group consisting of psychopharmaceuticals, analgesics and hormones. Particular substances which may be considered include estradiol as a hormone and buprenorphine as an analgesic. The psychopharmaceutical is preferably a parasympathomimetic.

Particularly suitable parasympathomimetics are the following:

1. choline esters, e.g. acetylcholine, bethanechol, carbachol or methacholine;
2. alkaloids, e.g. arecoline and its derivatives, pilocarpine;
3. choline esterase inhibitors, e.g. demacarium bromide, distigmine bromide, neostigmine, physostigmine, pyridostigmine bromide, galanthamine.

These substances can of course also be used in combinations with one another. The active substance content is set in particular such that when the plaster is removed there is what is known as a pulloff effect. This effect is explained hereinbelow:

Where a TTS includes a backing layer of limited water vapour permeability, such as a PET film, the skin is unable to give off water vapour at the application site while the TTS is being worn. This water becomes incorporated in the skin. At the application site, therefore, the water content is higher than the physiobiological norm. A substance which is difficult for the skin to absorb (such as buprenorphine, for example) becomes incorporated into a deposit in the skin. When the TTS is pulled off, the skin gives off water vapour suddenly. As a result of removal of this water, there is a sudden increase in the concentration of the medicament to above the saturation concentration, since solvent is removed. A stable state is reached by the rapid emptying of the skin deposit. Therefore, as a result of the TTS being pulled off, there is a rapid increase in the plasma concentration of the active substance. The utilization of the pulloff effect is preferred for better utilization of active substance. In accordance with the

invention, therefore, the concentration of the active substance is set such that the abovementioned pulloff effect comes about.

The absolute level of active substance for achieving the pulloff effect cannot generally be defined validly with precision. It varies from one active substance to another and also depends on the embodiment of the TTS. Setting of the level can, however, be undertaken by the person skilled in the art without undue burden by means of routine experiments. In the case of buprenorphine, the level is about 5 - 15% by weight.

The pressure-sensitive adhesive reservoir layer may also include a water-absorbing polymer. In one preferred embodiment, the water-absorbing polymer is a polyvinylpyrrolidone. The polyvinylpyrrolidone preferably has a molecular weight in the range from 1×10^3 to 2×10^6. Such polyvinylpyrrolidones include Kollidon®.

For special purposes, moreover, such as for use in hospitals with many patients or for use in double blind studies where TTS containing active substance are compared with placebo TTS, it is preferred for the side of the TTS that faces outwards - that is, away from the skin - to carry in the backing layer a marking/control element which is differentiated from the remaining area.

This element can differ from the remaining portion of the backing layer in its structure or in other properties, such as elasticity or porosity. By means of such a marking/control element the properties of the backing layer can be made different. For example, the elasticity of such an element can be greater than the elasticity of the remaining portion of the backing layer. If such a

marking/control element is specifically incorporated in one portion of the backing layer, then its relative elasticity - where desired - is preferably within a range situated about 20% below or about 20% above the elasticity of the remaining portion of the backing layer.

The marking/control element can also serve to distinguish the individual TTSs from one another in terms of their active substance content. This is done preferably by means of coloured marking, for example by means of a coloured thread or stripe. This is particularly advantageous if the TTS has to be held ready in large quantities at different dosages at one location: for example, a hospital with large numbers of patients.

The transdermal therapeutic system of the invention is particularly suitable for use as a multi-day plaster owing to its backing layer, which is tailored to this requirement. Thus it can be used in particular to treat chronic pain or else to treat drug dependency.

The TTS of the invention is produced by means of conventional processes. In general, such a process comprises the steps of producing the individual TTSs by punching from a presupplied strip-like laminate comprising the unidirectionally elastic backing layer of the invention, an active substance layer and a redetachable protective layer.

In one particularly preferred process for producing the TTS of the invention, the above steps are modified to the effect that, in a presupplied strip-like laminate having an optionally pressure-sensitive adhesive, unidirectionally elastic backing layer and a redetachable protective layer, pressure-sensitive adhesive active substance reservoir

sections are inserted in sequence in the longitudinal direction, the backing layer is separated by punching and then in the spaces between the active substance reservoir sections the protective layer is separated. This specific process has the feature that it is highly advantageous from both economic and environmental standpoints. Indeed, the separate insertion of the active substance reservoir sections avoids the formation of waste comprising active substance (which is usually very expensive) and thus the need to dispose - again at great expense - of such waste. A similar process is described in DE-B 41 10 027, which in this respect is expressly incorporated herein by reference.

The invention is elucidated below with reference to a drawing and an exemplary embodiment. In the figures,

Fig. 1 shows a plan view of the TTS of the invention;
Fig. 2 shows a section made at II-II through the TTS of Fig. 1.

Fig. 1 shows, diagrammatically, a plan view of a TTS of the invention. Lying atop the redetachable protective layer (1), which in the present case is rectangular, is the backing layer (5), which is coated with a pressure-sensitive adhesive devoid of active substance. It has the form of a rectangle with rounded corners. The punching line (1a) outlines the form of the backing layer (5). It extends outside the laminate comprising the reservoir (2) and, optionally, a barrier or separating layer (3). The course of the punching line means that loss of active substance is avoided when the patch is punched out. Within the backing layer (5) it is possible to make out the contours of the reservoir (2) and of the optional barrier layer (3).

In the TTS shown, with the unidirectionally elastic backing layer (5), the latter protrudes beyond the abovementioned laminate on all sides. The reservoir is preferably rectangular in form. The rectangular form is preferred since it enables losses of active substance to be avoided when the reservoir is cut.

Fig. 2 is a cross section through II-II of Fig. 1. For clarity, the thicknesses of the layers have been exaggerated. The TTS features the reservoir (2), the removable protective layer (1) and also the optional barrier layer (3) and a further layer (4) of pressure-sensitive adhesive devoid of active substance, this layer (4) being necessary when a barrier layer (3) is present. In this depicted embodiment, the backing layer (5) and the pressure-sensitive adhesive layer (4) devoid of active substance protrude beyond the abovementioned laminate on all sides.

Example

In order to produce the unidirectionally elastic backing layer of the invention, a woven polyester fabric having the following features was produced by means of the techniques known to the person skilled in the art.

TEST FEATURES	UNIT	Nominal	MIN	MAX	$\bar{X}$
WIDTH OF MATERIAL	mm	1500	1300	1390	1360
BASIS WEIGHT (unextended) (DIN 53854 + DIN 53884)	g/m^2	100	95	103	100
EXTENSION (longitudinal)	%	-	-	-	-
(transverse)	%	50	46	52	48
(DIN 61632)					
NUMBER OF WARP THREADS Per 10 cm unextended		320	310	330	324
NUMBER OF WEFT THREADS Per 10 cm unextended		125	124	126	124

In addition

49.175 kg of Durotak type 387-2054 (48.3% by weight solution)
4.450 kg of melted laevulinic acid and
6.675 kg of oleyl oleate

were homogenized with stirring. Then 4.450 kg of Kollidon 90F were added in portions. Following dilution with

6.800 kg of ethanol, the mixture was stirred at 170-190 rpm for 5 hours. Then 4.450 kg of buprenorphine base, suspended in 4.500 kg of ethyl acetate, were added. The mixture was diluted with 4.500 kg of ethyl acetate.

The mixture was stirred at 170 rpm for about 7 hours. It was then tested for homogeneity. When the composition was homogeneous it was devolatilized, with the stirrer switched off.

Following homogenization, the adhesive composition was applied to a siliconized polyester film. The organic solvents were removed by drying at normally 35°C to 80°C. The laminate, comprising siliconized polyester film and buprenorphine-containing pressure-sensitive adhesive layer, was subsequently covered with a second polyester film 23 μm thick.

The siliconized polyester film was removed from the resulting active substance laminate. Subsequently, rectangles measuring 50 cm^2 were punched out and were placed with their adhering face, at intervals of 3 cm, onto the siliconized face of a further 100 μm polyester protective film. Atop these reservoir sections was placed the unidirectionally elastic, woven polyester fabric, which in this case was likewise coated with pressure-sensitive adhesive. Subsequently, individual longitudinally elastic patches were punched out. A wearing test was conducted on n=10 subjects using this TTS of the invention.

<u>Comparative Example 1</u>

In this example, a bidirectionally elastic woven polyester fabric was used instead of the unidirectionally elastic woven polyester fabric of the invention. The extensibility of this fabric (longitudinal and transverse extension) was

30% as measured in accordance with DIN 61632. Its basis weight was 109 g/m². This material was a polyethylene terephthalate. In other respects, the TTSs produced in accordance with this comparative example were the same as those of the inventive example.

Using the TTSs according to this comparative example, a wear test was likewise conducted on n=10 subjects.

Comparative Example 2

TTSs were prepared in accordance with Example 1 and Comparative Example 1 but using a rigid polyester film (15 μm thick) of Hostaphan® RN 15, Hoechst AG, coated with pressure-sensitive adhesive, instead of a unidirectionally or bidirectionally elastic backing layer, respectively. In this case as well, a wear test was carried out with the resulting TTSs on n=10 subjects.

Evaluation

The comparative wear test of the TTSs of Example 1, Comparative Example 1 and Comparative Example 2 gave the following result:

When polyester film was used as the backing layer (Comparative Example 2), a sensation of a foreign body occurred on the very first day. On the second day, creasing occurred and, beginning on the third day, the TTS became detached. The TTS of Example 1 and that of Comparative Example 1 were worn without problems by all 10 subjects, with no sensation of a foreign body, with no impairment of bond strength, and, furthermore, with no skin irritations, for at least seven days. In respect of wear comfort, therefore, the TTS of Example 1 and that of Comparative Example 1 are approximately equal. However, with regard to the production of the TTS of Comparative Example 1,

complications in production occurred in a frequency of more than 50%, these complications being attributable predominantly to the curling effect.